Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 7, 2024

EFFECT OF CABERGOLINE ON GLUCOSE TOLERANCE AND WEIGHT IN PATIENTS WITH OBESITY

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Abstract

Introduction: Global obesity rates are rising due to rapid urbanisation and sedentary lifestyles, affecting health and economics. Modifications to one's way of life, medical interventions, and surgical procedures are among the methods that can be utilised to manage obesity. New dopaminergic drugs show promise, but regulatory hurdles remain. Dopamine modulation may reduce metabolic dysfunctions, but more research is needed.

Aim and objectives: This study aims to examine the impact of Cabergoline on glucose tolerance and weight in obese adults.

Method: The impact of cabergoline on blood glucose levels was examined in a double-blind research including 120 obese patients who were given either the active ingredient or a placebo. There was no statistically significant difference seen between the groups (P=0.792). Medications were delivered every week for 3 months in addition to the ongoing therapy. The study involved the implementation of fundamental laboratory tests and measures to continuously monitor the outcomes.

Result: This study presents the initial characteristics of the Cabergoline and Control groups, and compares them at 3 and 6 months. There were no notable disparities observed in terms of weight, waist circumference, blood pressure, or BMI. Once more, it examines the laboratory attributes before and following a 3-month therapy period, revealing that there are no notable disparities between the Cabergoline and Control groups in the majority of measures.

Conclusion: Cabergoline did not differ significantly from the control group in terms of weight, waist circumference, blood pressure, body mass index (BMI), or the majority of laboratory values after three months.

Keywords: Cabergoline, Obesity, blood pressure, glucose tolerance, “nucleus accumbens (NA)”.

INTRODUCTION

Rises in urbanization, sedentary lifestyles, and changes in physical activity levels have made obesity a major global health concern. A rise in sickness, impairment, and early death from a range of chronic diseases, including diabetes, tumors, muscle disorders, and heart maladies, has been attributed to this broad epidemic in recent decades. To make matters worse for the general public's health, obesity also increases the likelihood of metabolic disorders and cardiovascular problems. Obesity has severe economic and social costs in addition to negative effects on an individual's health, taxing both society and healthcare systems [1-4].

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 7, 2024

Globally, the prevalence of obesity has significantly increased in recent times, impacting people of all ages. This increasing tendency has been observed on a worldwide scale in a range of demographic and socioeconomic contexts. Over the years, there has been a consistent rise in the frequency of obesity, with notable increases noted after the year 1980. The fact that obesity rates are rising in both industrialized and developing countries highlights how pervasive the problem is [5,6]. Worldwide, being overweight has a substantial negative impact on both the economy and health. It has significant financial repercussions that put a strain on productivity and healthcare systems [7]. Numerous studies have demonstrated the significant financial cost of weight gain, with expenses varied by country. Obesity raises the risk of disability and lowers worker productivity besides contributing to direct medical expenses [8]. An elevated body mass index (BMI) of Forty kg/m^2 or more is indicative of severe obesity, which exacerbates these economic effects by increasing direct and productivity-related expenses. The economic effects of obesity are predicted to worsen as the disease's prevalence rises, creating problems for society's well-being and healthcare spending [9].

A variety of strategies are used in the management of weight gain, including modifications to behavior, pharmaceuticals, and surgeries. To tackle the persistent and recurrent character of obesity, the emphasis is on promoting long-term lifestyle modifications [10]. Long-term medical monitoring and the application of evidence-based practices customized to each patient's needs are frequently necessary for an effective course of treatment. However, obstacles in healthcare settings can prevent the best possible treatment for obesity from being provided [11]. New anti-obesity drugs show potential and enhance current treatment approaches. In addition to weight loss, treatment objectives prioritize improving general health and lowering the risk of cardiometabolic diseases [12]. Among the evidence-based strategies used are bariatric surgery, medication, lifestyle changes, and formula diets. A cooperative, diverse team approach is necessary for comprehensive care of obesity due to its complexity. In the end, changing one's lifestyle is still essential for maintaining a healthy weight throughout life as well as preventing and treating it [13].

Finding efficient treatment plans is crucial when it comes to managing obesity. While previous safety issues and low effectiveness have plagued existing pharmaceutical methods, emerging medications show signs of promise. It is evident, therefore, that no single drug will offer a cure for all problems. Going forward, one possible path would be to seek approval for drugs that address problems associated with being overweight. However, there are still obstacles to the use of pharmacotherapy, including attitudes held by physicians and patients, regulatory obstacles, and payment restrictions. Positive signs point to the possibility that government initiatives will soon expand the payment pool for anti-obesity drugs. Moreover, creative approaches that integrate medical technology with service delivery can revolutionize the field of treating obesity [12,14,15].

It is becoming clear that dopaminergic pathways are important in the control of obesity. In the nucleus accumbens (NA), a part of the brain involved in reward processing, aerobic activity, for example, has been linked to increased dopamine levels, which in turn enhances food reward in obese patients [16]. Furthermore, a sedentary lifestyle commonly associated with obesity has been linked to deficiencies in striatal D2 receptor activation [17]. These pathways play a significant role in controlling the inflammatory environment linked to

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 7, 2024

obesity by precisely regulating food habits and appetite [18]. The metabolic dysfunctions associated with obesity may be ameliorated by pharmacological therapies that target dopamine regulation, such as bromocriptine [19]. Specifically, deep brain stimulation that targets the NA periphery has shown promise in lowering total calorie intake and alleviating binge eating episodes [20]. Notwithstanding these developments, more research is necessary to completely clarify the curative value of dopamine-based therapies in the all-encompassing handling of adiposity [21].

Dopamine agonist cabergoline has attracted attention due to its possible experimental effects on the breakdown of glucose and calorie management in obese persons. According to research, people with type 2 diabetes and prediabetes may benefit from cabergoline's positive effects on the processing of glucose. Nevertheless, it does not seem to be very effective in keeping obese people from gaining weight back after losing it. The motivation behind the investigation of the substance in overweight is its possible capacity to regulate dopamine receptors, which could potentially improve metabolic parameters linked to overweight [22-24].

The aim of this study is to assess the impact of Cabergoline on glucose tolerance and weight in obese adults. Its advantage lies in exploring a potential new treatment avenue for obesity, leveraging dopaminergic modulation, which could address metabolic dysfunctions associated with obesity and provide alternative therapeutic options.

Method

Research Design

This was a double-blind clinical trial to assess cabergoline's effect on blood glucose levels in patients referred to our obesity patients by using a placebo as the control. The 120 patients were randomly randomised to either the control or cabergoline groups, with the place defined by power and index of assurance calculations. A significant difference ($P<0.05$) in glycosylated haemoglobin (HbA1C) was used to determine the classification. Each group comprised 60 males and 60 females. All patients obtained informed permission before starting this trial. Patients' age, sex, weight, height, waist circumference, diabetes duration, and medicines were recorded. Glibenclamide and Metformin and Metformin and Acarbose were given to participants in this treatment. In addition, other patients received Metformin, Glibenclamide, and Pioglitazone, while received Glibenclamide, Metformin, and Acarbose. The study found no significant difference between the two groups ($P=0.792$). Further, the patients were given at least half of the maximum dose of their prior drugs. Weight was accurately measured at 100g using the SECA scale. Fabric meters were used to measure the waist length around the navel. The patient's blood pressure was taken by a trained nurse using a reliable Microlife device. Weight, blood pressure, and waist circumference were measured after 3 and 6 months. Patients' basic laboratory tests, such as FBS, 2HPP, complete lipid profile, serum insulin, prolactin, Hb, ALT, AST, Cr, and BUN, were monitored at treatment start and 3, 6, and 9 months. Patients having HbA1C values $\leq$7% after 3 months were excluded from the trial. Patients having HbA1C levels ranging from 7% to 10% were treated with cabergoline (0.5 mg) or placebo twice a week for 3 months. ELISA was used to assess cabergoline's effects on insulin sensitivity and prolactin levels. All patients' venous blood samples were centrifuged for 10 minutes at 3000r/min. Our Indian hospital designed the medicine and placebo in this trial, and they should be equivalent in shape, size, colour, and packaging. Pharmacologists in this department named and coded medications and placebos

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but did not prescribe them. Furthermore, a nurse who helped the researchers with the study provided the patients with random deliveries of the coded medications (cabergoline) and placebos. The patients were administered either a placebo or cabergoline (0.5 mg) orally once a week for a duration of 3 months. They continued to take their previously prescribed glucose-lowering medications during this period.

Inclusion and Exclusion Criteria

Inclusion

- Type 2 diabetes is diagnosed at least 3 months before the trial.
- Treatment with two oral glucose-lowering medicines at 50% of the maximum recommended dose.
- The age range is between 20 and 80 years old.
- HbA1C levels that are equal to or less than 10%.
- Reproductive-age women had to use reliable contraception during the trial.

Exclusion

- Patients who were unwilling to take part in the research project.
- Pregnancy or breastfeeding are both options.
- Uncontrolled thyroid issues.
- A creatinine level of over 2 mg/dL.
- Current meds that dramatically alter blood sugar

Statistical analysis

The statistical software SPSS, version 27, was used to analyse the study data. To statistically assess the information in both groups, a Student's t-test was used. To compare the before and after treatment results in each group, a paired t-test was employed. The P-value was computed using a level of significance of 0.05 as the unit of measurement.

Result

Table 1 shows patient demographics, including weight, waist circumference, systolic and diastolic blood pressure, and BMI at baseline, 3 months, and 6 months. The baseline evaluation showed a mean weight of 79.2 kg for the Cabergoline group, with a standard deviation of ±12.1, compared to 80.56 kg with ±9.30 for the Control group. The statistical significance of the weight difference between the two groups was not established ($p = 0.649$). For waist circumference, the Cabergoline group (106.2 cm) and the Control group (106.2 cm) had similar mean values ($p = 0.499$). At baseline, the Cabergoline group had a mean systolic blood pressure of 119.2 mm Hg with a standard deviation of ±11.8. In comparison, the Control group had a little lower mean of 115.6 mm Hg with a standard deviation of ±10.8. Systolic blood pressure differed significantly between groups ($p = 0.021$). The Cabergoline group had a significantly higher mean diastolic blood pressure (80.1 mm Hg (±8.1)) than the Control group (79.5 mm Hg (±8.6) ($p = 0.030$).

The baseline BMI measurements of the Cabergoline and Control groups were similar, with averages of 29.8 kg/m^2 and 29.7 kg/m^2, respectively ($p = 0.950$). At 3- and 6-month follow-ups, similar comparisons were done for each measure, and the statistical significance (or lack thereof) of the differences between the Cabergoline and Control groups was reported. On weight, waist circumference, blood pressure, and BMI, the Cabergoline and Control groups did not vary at 3- or 6-month intervals, according to the p-values. Table 1 shows

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baseline weight, waist circumference, blood pressure, and BMI for the Cabergoline and Control groups, as well as statistical comparisons at each time point.

Table 1: Demographic details of patients

	Base			**After 3 months**			**After 6 months**		
	Cabergoline group	Control group	p value	Cabergoline group	Control group	p value	Cabergoline group	Control group	p value
Variable	mean ± SD	mean ± SD		mean ± SD	mean ± SD		mean ± SD	mean ± SD	
Weight, kg	79.2±12.1	80.56 ±9.30	0.649	79.5± 12.3	79.3± 9.8	0.450	79.3± 13.7	80.1± 9.9	0.849
Waist circumference, cm	106.2± 11.8	106.2 ±7.01	0.499	108.2 ±11.8	106.8 ±8.1	0.569	108.6 ±15.9	108.2 ±8.8	0.979
Systolic blood pressure, mm Hg	119.2± 11.8	115.6 ±10.8	0.021	119.2 ±11.7	117.2 ±8.8	0.119	117.2 ±4.9	113.2 ±4.9	0.179
Diastolic blood pressure, mm Hg	80.1±8.1	79.5± 8.6	0.030	80.1± 7.9	75.2± 6.9	0.629	69.8± 8.9	69.8± 5.1	0.549
BMI, kg/m^2	29.8±5.9	29.7± 6.2	0.950	29.8± 5.9	29.8± 5.6	0.760	29.9± 8.1	29.8± 5.1	0.719

Table 2 compares before and after 3 months of treatment for Cabergoline and Control patients' laboratory characteristics. The table includes fasting blood sugar (FBS), 2-hour postprandial (2HPP) blood sugar, HbA1C, cholesterol (total, LDL, HDL), triglycerides, BUN, Cr, AST, ALT, insulin, prolactin, and HOMA-IR. Prior to treatment, the average fasting blood sugar levels were 155.09 mg/dL in the Cabergoline group and 181.09 mg/dL in the Control group. The three-month treatment period resulted in a small rise in both groups, with average levels of 156.09 and 181.09 mg/dL, respectively.

Prior to treatment, the two groups' p-values were 0.061, indicating a trend towards significance; however, three months later, the p-value was 0.829, indicating no significant difference between the groups. Cabergoline and Control groups were compared prior to and after treatment for 2-hour postprandial blood sugar, HbA1C, cholesterol (total, LDL, HDL), triglycerides, BUN, Cr, AST, ALT, insulin, prolactin, and HOMA-IR. Most p-values showed no significant differences between the two groups at either time point. On the other hand, there were a few notable exceptions. ALT levels, for example, were significantly different between the Cabergoline and Control groups before treatment ($p = 0.021$), with mean levels of 20 U/L and 19 U/L, respectively. The observed disparity did not reach statistical significance over a 3-month course of treatment ($p = 0.111$).

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Furthermore, there was a notable disparity in prolactin levels between the two groups prior to treatment (p = 0.030), with average values of 4.39 ng/mL in the Cabergoline group and 6.39 ng/mL in the Control group. The observed difference lost its statistical significance after 3 months of treatment (p = 0.509). Table 2 shows any significant variations in biochemical parameters between Cabergoline-treated and control participants before and after 3 months.

Table 2: Laboratory characteristics of the patients before and after 3 months of treatment.

	Cabergoline group			**Control group**			**P-value***	
	Brefore treatment	3 months after treatment		Brefore treatment	3 months after treatment		Brefore treatment 3 months after treatment	Control group
	mean ± SD	mean ± SD	p value	mean ± SD	mean ± SD	p value	mean ± SD	mean ± SD
FBS, mg/dL	155.09±39	156.09±39	0.061	181.09±39	181.09±39	0.829	0.060	0.003
2HPP, mg/dL	245.61±80.50	248.59±80.49	0.058	270.61±80.50	269.59±80.49	0.699	0.059	0.039
HbA1C, %	8.95±1.40	8.98±1.39	0.369	7.95±1.40	7.98±1.39	0.071	0.370	0.249
Cholestrol, mg/dL	179.79±19.23	179.80±19.19	0.941	169.79±19.23	169.80±19.19	0.621	0.940	0.261
LDL, mg/dL	80.85±21.39	81.88±21.40	0.129	79.85±21.39	79.88±21.40	0.099	0.130	0.131
HDL, mg/dL	50.65±19.69	51.69±19.70	0.068	49.65±19.69	49.69±19.70	0.059	0.069	0.809
Triglycerides, mg/dL	170.69±40.75	169.71±39.88	0.609	150.69±40.75	149.71±39.88	0.861	0.610	0.571
BUN, mg/dL	21.79±7.85	20.81±7.88	0.685	20.79±7.85	19.81±7.88	0.06	0.688	0.911
Cr, mg/dL	0.80±0.09	0.79±0.09	0.494	0.80±0.09	0.79±0.09	0.311	0.499	0.109
AST, U/L	19.70±5.10	1+.69±5.09	0.375	20.70±5.10	19.69±5.09	0.679	0.370	0.981
ALT, U/L	20±5.09	19±5.09	0.021	20±5.09	19±5.09	0.111	0.020	0.491
Insulin, U/L	7.61±4.4.91	7.59±4.4.89	0.874	7.61±4.4.91	7.59±4.4.89	0.31	0.870	0.469
Prolactin, ng/mL	4.39±3.01	4.41±3.01	0.365	6.39±3.01	6.41±3.01	0.509	0.369	0.030
HOMA-IR	2.20±1.79	2.21±1.80	0.496	3.20±1.79	3.21±1.80	0.931	0.499	0.579

*between 2 groups

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 7, 2024

Discussion

A variety of medical disorders are treated using the dopaminergic agonist cabergoline. It produces prolonged dopaminergic action by activating dopamine receptors. Its uses in medicine include treating hyperprolactinemia, the disorder Parkinson's, a disorder of the legs, and prolactin increase brought on by drugs. Moreover, cabergoline shows promise in the treatment of acromegaly, movement problems, and Cushing's disease [25-27]. It binds to dopamine receptors in the brain, particularly D2 receptors, to perform the function of a dopamine receptor agonist. It functions as a transmitter at human recombinant 5HT(2), 5HT(1A), and D(2/3) receptors and demonstrates a high affinity for dopamine D2-like receptors [28].

Numerous studies show that cabergoline has potential effects on the metabolism of glucose. Studies show that in people with prediabetes, cabergoline improves glucose metabolism and increases glucose tolerance without affecting weight loss [29]. Furthermore, cabergoline therapy is linked to appreciable drops in plasma glucose concentrations at rest in prolactinoma patients [22]. Similarly, cabergoline improves glycemic control in patients with type 2 diabetes who have failed oral agents by lowering HbA1c and plasma glucose levels during fasting and postprandial periods [30]. These results are corroborated by a meta-analysis and review of the literature conducted by Andersen et al. (2021), which found that dopamine agonists, such as cabergoline, lower HbA1c, and plasma glucose levels at rest in people with type two diabetes [31]. The combined findings point to a possible benefit of cabergoline [29-31].

The effect of cabergoline on an obese person's body weight has been studied. In obese non-diabetic people, research by Gibson et al. (2012) shows that cabergoline medication improves their ability to tolerate glucose without affecting changes in body weight [29]. Moreover, treatment was linked to notable decreases in waist measurement, weight, BMI, and total fat mass in prolactinoma patients [19]. Furthermore, research conducted on obese participants by Pala et al. (2015) showed that cabergoline administration led to significant reductions in body weight and body fat when compared to placebo [33]. Based on these results, it appears that cabergoline may help obese people lose weight [33].

Treatment with the substance has been associated with weight changes because of its effects on metabolic variables. Studies conducted by Manning et al. (2018) indicate that the substance may cause weight loss and improvements in body composition, which are especially noticeable in prolactinoma patients [23]. Moreover, cabergoline has been shown to help with lipid levels, tolerance to insulin, and the utilization of glucose [33]. However, cabergoline did not appear to have any appreciable effect on preventing weight rebound in a trial by Posawetz et al. (2021) that focused on maintaining weight reduction [34]. All things considered, cabergoline's impact on weight fluctuations is probably mediated by its actions on several physiological parameters, such as insulin responsiveness, cholesterol levels, and the breakdown of glucose [33, 34].

Following research by Aboelnaga et al. (2019), people with both prediabetes and type 2 diabetes who take cabergoline have enhanced the absorption of glucose. Moreover, it has been effective in helping obese people lose weight while enhancing their blood sugar sensitivity. In patients with a high level of it proved efficacy in enhancing overall biochemical and morphological variables when compared to alternative methods and drugs for weight management [35].

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Dopamine signaling pathways are the mechanism by which the drug acts, and they are essential in controlling sensations of appetite and fullness. In particular, dopamine affects how hunger is controlled by interacting with the D1 and D2 receptors in particular areas of the brain. It may influence these receptors through its dopamine agonist action, which could affect eating habits [36, 37]. Intricate neurobiological networks that communicate with monoamines, which in the brain's hypothalamus to control starvation, fulfillment, and contentment include pro-opiomelanocortin and neuropeptide Y (NPY). These pathways are also involved in the regulation of appetite. To find viable treatment targets for obesity, it is crucial to comprehend the complexity of these interactions [38, 39].

Some knowledge gaps need to be filled in, such as the examination of customized methods for addressing overweight and the long-term effects of the drug on maintaining loss of weight. Its impact on response to insulin and physiological variables makes it a possible component of customized obesity management plans. However, further investigation is required to fully understand its long-term impacts and its role in customized weight loss therapy [23,30,40].

Conclusion

This study concluded that the findings of the study indicate that the administration of cabergoline did not result in any significant differences when compared to the control group in terms of weight, waist circumference, blood pressure, body mass index (BMI), or the majority of laboratory parameters after a period of three months passed. Pre-treatment variations in systolic and diastolic blood pressure, ALT levels, and prolactin concentrations did not persist or become significant after 3 months. Overall, the results suggest that Cabergoline administration did not cause significant changes in the measured parameters when compared to the control group within the stipulated period. Additional longitudinal studies with bigger sample sizes are necessary to confirm these findings and investigate the potential long-term impacts of Cabergoline administration. Despite the initial hypothesis, this study found no significant differences between the Cabergoline and control groups in weight, glucose tolerance, or other metabolic parameters after three months. This indicates a research gap in understanding the efficacy of Cabergoline in managing obesity. Future research could focus on longer treatment durations, larger sample sizes, or combination therapies involving Cabergoline to elucidate its potential benefits further. Additionally, exploring the underlying mechanisms of dopaminergic modulation in metabolic regulation could pave the way for novel therapeutic approaches targeting obesity and related metabolic disorders. Further investigations into the interaction between Cabergoline and other metabolic pathways may also unveil new avenues for intervention in obesity management

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